

WHAT IS CLAIMED IS:

1. A multi-binding compound comprising 2 to 10 ligands which may be the same or different and which are covalently attached to a linker or linkers, which may be the same or different, each of said ligands comprising a ligand domain capable of binding to a cell membrane transporter, with the following provisos:

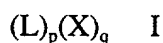
(a) when each ligand is a 1,2,3,4 tetrahydroisoquinoline, then the linker is at least two atoms;

(b) neither the compound nor the ligand is a bis-quinolinium cyclophane; and

(c) the multibinding compound does not comprise homomeric phenylsulfonamide ligands;

(d) the multibinding compound does not comprise a dimeric 1,4 dihydropyridine compound linked through carboxylic ester groups.

2. A multi-binding compound represented by formula I:



where each L is a ligand that may be the same or different at each occurrence;

X is a linker that may be the same or different at each occurrence;

p is an integer of from 2 to 10; and

q is an integer of from 1 to 20;

wherein each of said ligands comprises a ligand domain capable of binding to a cell membrane transporter, with the following provisos:

(a) when each ligand is a 1,2,3,4 tetrahydroisoquinoline, then the linker is at least two atoms;

(b) neither the compound nor the ligand is a bis-quinolinium cyclophane; and

(c) the multibinding compound does not comprise homomeric phenylsulfonamide ligands;

(d) the multibinding compound does not comprise a dimeric 1,4 dihydropyridine compound linked through carboxylic ester groups.

3. The multi-binding compound of Claim 2, wherein q is less than p .

4. The multibinding compound according to Claim 1 or Claim 2 wherein the compound is dimeric.

5. The multibinding compound according to Claim 4 wherein the dimeric compound is heterodimeric.

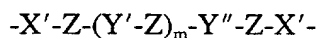
6. The multibinding compound according to Claim 1 or Claim 2 wherein the linker or linkers employed are selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic linkers, basic linkers, linkers of different polarization and/or polarizability and amphiphilic linkers.

7. The multibinding compound according to Claim 6 wherein the linkers comprise linkers of different chain length and/or having different complementary reactive groups.

8. The multibinding compound according to Claim 7 wherein the linkers are selected to have different linker lengths ranging from about 2 to 100Å.

9. The multibinding compound according to Claim 8 wherein the linkers are selected to have different linker lengths ranging from about 3 to 40Å.

10. The multibinding compound according to Claim 1 or 2 wherein the linker is represented by the formula::



in which:

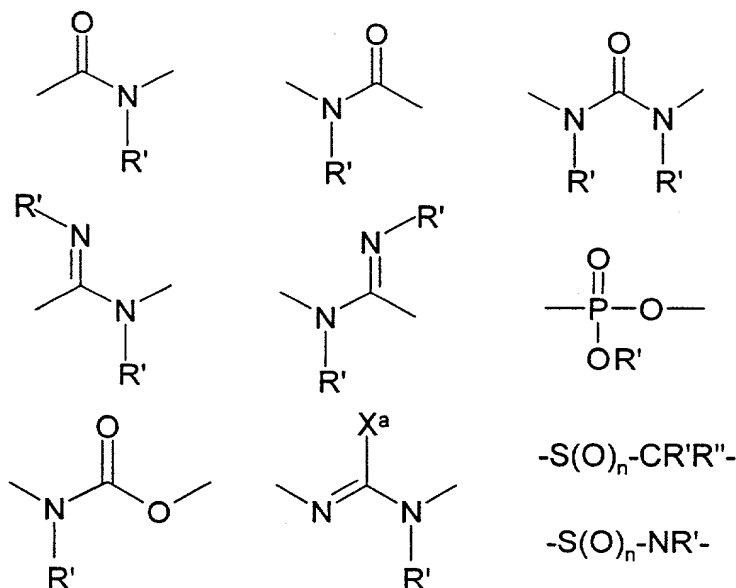
m is an integer of from 0 to 20;

5 X' at each separate occurrence is selected from the group consisting of -O-, -S-, -NR-, -C(O)-, -C(O)O-, -C(O)NR-, -C(S), -C(S)O-, -C(S)NR- or a covalent bond where R is as defined below;

10 Z is at each separate occurrence is selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, heteroarylene, heterocyclene, or a covalent bond;

Y' and Y'' at each separate occurrence are selected from the group consisting of

:



15 in which:

n is 0, 1 or 2; and

R, R' and R'' at each separate occurrence are selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic.

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11. The multibinding compound according to Claim 4 wherein the dimeric compound is homodimeric.

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12. The multibinding compound according to Claim 11 wherein the two cell membrane transporter ligands are linked to the homodimeric compound at the same point on the ligand.

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13. The multibinding compound according to Claim 10 wherein the two cell membrane transporter ligands are linked to the homodimeric compound at different points on the ligand.

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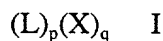
14. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a therapeutically effective amount of one or more multi-binding compounds, or pharmaceutically acceptable salts thereof, comprising 2 to 10 ligands which may be the same or different and which are covalently attached to a linker or linkers, which may be the same or different, each of said ligands comprising a ligand domain capable of binding to a cell membrane transporter of a cell mediating mammalian or avian diseases or conditions, thereby modulating the diseases or conditions, with the following provisos:

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- (a) when each ligand is a 1,2,3,4 tetrahydroisoquinoline, then the linker is at least two atoms;
- (b) neither the compound nor the ligand is a bis-quinolinium cyclophane; and
- (c) the multibinding compound does not comprise homomeric phenylsulfonamide ligands;

(d) the multibinding compound does not comprise a dimeric 1,4 dihydropyridine compound linked through carboxylic ester groups.

15. A pharmaceutical composition comprising a pharmaceutically acceptable
5 excipient and a therapeutically effective amount of one or more multi-binding compounds represented by formula I,



10 and pharmaceutically acceptable salts thereof,
where each L is a ligand that may be the same or different at each occurrence;
X is a linker that may be the same or different at each occurrence;
p is an integer of from 2 to 10; and
q is an integer of from 1 to 20;
15 wherein each of said ligands comprises a ligand domain capable of binding to a cell membrane transporter of a cell mediating mammalian or avian diseases or conditions, thereby modulating the diseases or conditions, with the following provisos:
(a) when each ligand is a 1,2,3,4 tetrahydroisoquinoline, then the linker is at least two atoms;
20 (b) neither the compound nor the ligand is a bis-quinolinium cyclophane; and
(c) the multibinding compound does not comprise homomeric phenylsulfonamide ligands;
(d) the multibinding compound does not comprise a dimeric 1,4 dihydropyridine compound linked through carboxylic ester groups.

25 16. The pharmaceutical composition according to Claim 15 wherein q is less than p.

17. The pharmaceutical composition according to Claim 14 or Claim 15 wherein the compound is dimeric.

18. The pharmaceutical composition according to Claim 17 wherein the dimeric compound is heterodimeric.

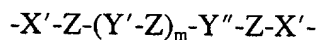
19. The pharmaceutical composition according to Claim 14 or Claim 15 wherein the linker or linkers employed are selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic linkers, basic linkers, linkers of different polarization and/or polarizability and amphiphilic linkers.

20. The pharmaceutical composition according to Claim 19 wherein the linkers comprise linkers of different chain length and/or having different complementary reactive groups.

21. The pharmaceutical composition according to Claim 20 wherein the linkers are selected to have different linker lengths ranging from about 2 to 100Å.

22. The pharmaceutical composition according to Claim 21 wherein the linkers are selected to have different linker lengths ranging from about 3 to 40Å.

23. The pharmaceutical composition according to Claim 14 or 15 wherein the linker is represented by the formula::



in which:

m is an integer of from 0 to 20;

Z is at each separate occurrence is selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, heteroarylene, heterocyclene, or a covalent bond;

Chemical structures of various amide and imine derivatives:

- Structure 1: $\text{CH}_3\text{C}(=\text{O})\text{N}(\text{CH}_3)\text{R}'$
- Structure 2: $\text{CH}_3\text{C}(=\text{O})\text{N}(\text{R}')\text{CH}_3$
- Structure 3: $\text{CH}_3\text{C}(=\text{O})\text{N}(\text{R}')\text{C}(\text{CH}_3)\text{N}(\text{R}')\text{CH}_3$
- Structure 4: $\text{CH}_3\text{C}(\text{N}(\text{R}')\text{CH}_3)=\text{N}(\text{R}')$
- Structure 5: $\text{CH}_3\text{C}(\text{N}(\text{R}')\text{CH}_3)=\text{N}(\text{R}')\text{CH}_3$
- Structure 6: $\text{CH}_3\text{C}(=\text{O})\text{OCH}_3$
- Structure 7: $\text{CH}_3\text{C}(\text{X}^a)=\text{N}(\text{R}')\text{CH}_3$
- Structure 8: $-\text{S}(\text{O})_n-\text{CR}'\text{R}''-$
- Structure 9: $-\text{S}(\text{O})_n-\text{NR}'-$

in which:

R, R' and R'' at each separate occurrence are selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic.

15 substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic.

24. A method for modulating the activity of a cell membrane transporter in a biologic tissue, which method comprises contacting a tissue having a cell membrane transporter with a multi-binding compound, or a pharmaceutically acceptable salt thereof, under conditions sufficient to produce a change in transporter activity in said tissue, wherein the multi-binding compound comprises 2 to 10 ligands which may be the same or different and which are covalently attached to a linker or linkers, which may be the same or different, each of said ligands comprising a ligand domain capable of binding to a cell membrane transporter, with the following provisos:

(a) when each ligand is a 1,2,3,4 tetrahydroisoquinoline, then the linker is at least two atoms;

(b) neither the compound nor the ligand is a bis-quinolinium cyclophane; and

(c) the multibinding compound does not comprise homomeric phenylsulfonamide ligands;

(d) the multibinding compound does not comprise a dimeric 1,4 dihydropyridine compound linked through carboxylic ester groups.

25. A method for treating a disease or condition in a mammal or avian resulting from an activity of a cell membrane transporter, which method comprises administering to said mammal or avian a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable excipient and one or more multi-binding compounds, or pharmaceutically acceptable salts thereof, comprising 2 to 10 ligands which may be the same or different and which are covalently attached to a linker or linkers, which may be the same or different, each of said ligands comprising a ligand domain capable of binding to a cell membrane transporter of a cell mediating mammalian or avian diseases or conditions, with the following provisos:

(a) when each ligand is a 1,2,3,4 tetrahydroisoquinoline, then the linker is at least two atoms;

(b) neither the compound nor the ligand is a bis-quinolinium cyclophane; and

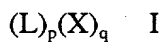
(c) the multibinding compound does not comprise homomeric phenylsulfonamide ligands;

(d) the multibinding compound does not comprise a dimeric 1,4 dihydropyridine compound linked through carboxylic ester groups.

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26. A method for treating a disease or condition in a mammal or avian resulting from an activity of a cell membrane transporter, which method comprises administering to said mammal or avian a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable excipient and one or more multibinding compounds represented by formula I,

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and pharmaceutically acceptable salts thereof,

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where each L is a ligand that may be the same or different at each occurrence;

X is a linker that may be the same or different at each occurrence;

p is an integer of from 2 to 10; and

q is an integer of from 1 to 20;

wherein each of said ligands comprises a ligand domain capable of binding to a cell membrane transporter of a cell mediating mammalian or avian diseases or conditions, with the following provisos:

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(a) when each ligand is a 1,2,3,4 tetrahydroisoquinoline, then the linker is at least two atoms;

(b) neither the compound nor the ligand is a bis-quinolinium cyclophane; and

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(c) the multibinding compound does not comprise homomeric phenylsulfonamide ligands;

(d) the multibinding compound does not comprise a dimeric 1,4 dihydropyridine compound linked through carboxylic ester groups.

27. The method according to Claim 26 wherein q is less than p .

28. The method according to Claim 24, Claim 25 or Claim 26 wherein the compound is dimeric.

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29. The method according to Claim 28 wherein the dimeric compound is heterodimeric.

30. The method according to Claim 28 wherein the dimeric compound is homodimeric.

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31. The method according to Claim 24, Claim 25 or Claim 26 wherein the linker or linkers employed are selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic linkers, basic linkers, linkers of different polarization and/or polarizability and amphiphilic linkers.

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32. The method according to Claim 31 wherein the linkers comprise linkers of different chain length and/or having different complementary reactive groups.

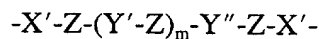
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33. The method according to Claim 32 wherein the linkers are selected to have different linker lengths ranging from about 2 to 100Å.

34. The method according to Claim 33 wherein the linkers are selected to have different linker lengths ranging from about 3 to 40Å.

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35. The method compound according to Claim 24, Claim 25 or Claim 26 wherein the linker is represented by the formula:



in which:

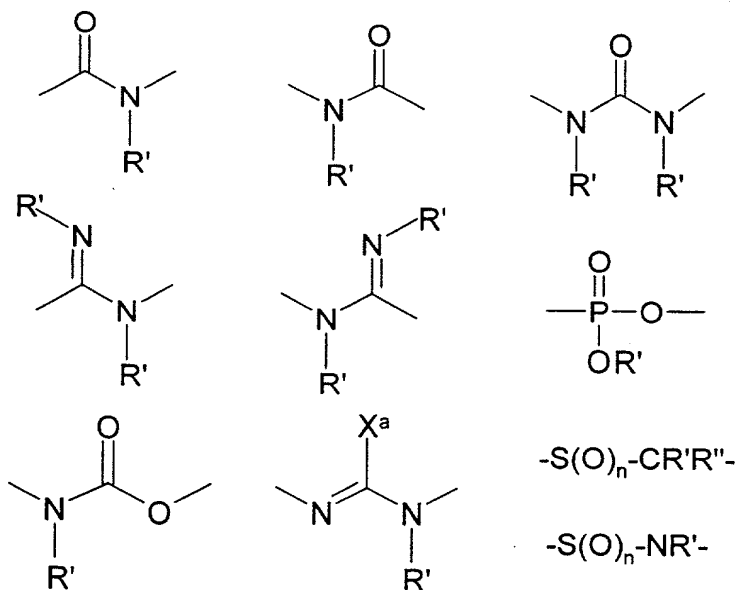
m is an integer of from 0 to 20;

5 X' at each separate occurrence is selected from the group consisting of -O-, -S-, -NR-, -C(O)-, -C(O)O-, -C(O)NR-, -C(S), -C(S)O-, -C(S)NR- or a covalent bond where R is as defined below;

10 Z is at each separate occurrence is selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, heteroarylene, heterocyclene, or a covalent bond;

Y' and Y'' at each separate occurrence are selected from the group consisting of

:



-S-S- or a covalent bond;

15 in which:

n is 0, 1 or 2; and

R, R' and R'' at each separate occurrence are selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic.

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36. A method for identifying multimeric ligand compounds possessing multibinding properties which method comprises:

(a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality;

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(b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;

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(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and

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(d) assaying the multimeric ligand compounds produced in the library prepared in (c) above to identify multimeric ligand compounds possessing multibinding properties.

37. A method for identifying multimeric ligand compounds possessing multibinding properties which method comprises:

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(a) identifying a library of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a linker or mixture of linkers wherein each linker comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and

(d) assaying the multimeric ligand compounds produced in the library prepared in (c) above to identify multimeric ligand compounds possessing multibinding properties.

38. The method according to Claim 36 or 37 wherein the preparation of the multimeric ligand compound library is achieved by either the sequential or concurrent combination of the two or more stoichiometric equivalents of the ligands identified in (a) with the linkers identified in (b).

39. The method according to Claim 38 wherein the multimeric ligand compounds comprising the multimeric ligand compound library are dimeric.

40. The method according to Claim 39 wherein the dimeric ligand compounds comprising the dimeric ligand compound library are heterodimeric.

41. The method according to Claim 39 wherein the dimeric ligand compounds comprising the dimeric ligand compound library are heterodimeric.

42. The method according to Claim 39 wherein the heterodimeric ligand compound library is prepared by sequential addition of a first and second ligand.

43. The method according to Claim 36 or 37 wherein, prior to procedure (d), each member of the multimeric ligand compound library is isolated from the library.

44. The method according to Claim 43 wherein each member of the library is isolated by preparative liquid chromatography mass spectrometry (LCMS).

45. The method according to Claim 36 or Claim 37 wherein the linker or linkers employed are selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic linkers, basic linkers, linkers of different polarization and/or polarizability and amphiphilic linkers.

46. The method according to Claim 45 wherein the linkers comprise linkers of different chain length and/or having different complementary reactive groups.

47. The method according to Claim 46 wherein the linkers are selected to have different linker lengths ranging from about 2 to 100Å.

48. The method according to Claim 36 or 37 wherein the ligand or mixture of ligands is selected to have reactive functionality at different sites on said ligands.

49. The method according to Claim 48 wherein said reactive functionality is selected from the group consisting of carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, pseudohalides, isocyanates, vinyl unsaturation, ketones, aldehydes, thiols, alcohols, anhydrides, boronates, and precursors thereof wherein the reactive functionality on the ligand is selected to be complementary to at least one of the reactive groups on the linker so that a covalent linkage can be formed between the linker and the ligand.

50. The method according to Claim 36 or Claim 37 wherein the multimeric ligand compound library comprises homomeric ligand compounds.

51. The method according to Claim 36 or Claim 37 wherein the multimeric ligand compound library comprises heteromeric ligand compounds.

52. A library of multimeric ligand compounds which may possess multivalent properties which library is prepared by the method comprising:

(a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

53. A library of multimeric ligand compounds which may possess multivalent properties which library is prepared by the method comprising:

(a) identifying a library of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a linker or mixture of linkers wherein each linker comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

54. The library according to Claim 52 or Claim 53 wherein the linker or linkers employed are selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic linkers, basic linkers, linkers of different polarization and/or polarizability and amphiphilic linkers.

55. The library according to Claim 54 herein the linkers comprise linkers of different chain length and/or having different complementary reactive groups.

56. The library according to Claim 55 herein the linkers are selected to have different linker lengths ranging from about 2 to 100Å.

57. The library according to Claim 52 or 53 wherein the ligand or mixture of ligands is selected to have reactive functionality at different sites on said ligands.

58. The library according to Claim 57 wherein said reactive functionality is selected from the group consisting of carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, pseudohalides, isocyanates, vinyl unsaturation, ketones, aldehydes, thiols, alcohols, anhydrides, boronates, and precursors thereof wherein the reactive functionality on the ligand is selected to be complementary to at least one of the reactive groups on the linker so that a covalent linkage can be formed between the linker and the ligand.

59. The library according to Claim 52 or Claim 53 wherein the multimeric ligand compound library comprises homomeric ligand compounds.

60. The library according to Claim 52 or Claim 53 wherein the multimeric ligand compound library comprises heteromeric ligand compounds.

61. An iterative method for identifying multimeric ligand compounds possessing multibinding properties which method comprises:

5 (a) preparing a first collection or iteration of multimeric compounds which is prepared by contacting at least two stoichiometric equivalents of the ligand or mixture of ligands which target a receptor with a linker or mixture of linkers wherein said ligand or mixture of ligands comprises at least one reactive functionality and said linker or mixture of linkers comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand wherein said contacting is conducted under conditions wherein the complementary
10 functional groups react to form a covalent linkage between said linker and at least two of said ligands;

(b) assaying said first collection or iteration of multimeric compounds to assess which if any of said multimeric compounds possess multibinding properties;

15 (c) repeating the process of (a) and (b) above until at least one multimeric compound is found to possess multibinding properties;

(d) evaluating what molecular constraints imparted or are consistent with imparting multibinding properties to the multimeric compound or compounds found in the first iteration recited in (a)- (c) above;

20 (e) creating a second collection or iteration of multimeric compounds which elaborates upon the particular molecular constraints imparting multibinding properties to the multimeric compound or compounds found in said first iteration;

(f) evaluating what molecular constraints imparted or are consistent with imparting enhanced multibinding properties to the multimeric compound or compounds found in the second collection or iteration recited in (e) above;

25 (g) optionally repeating steps (e) and (f) to further elaborate upon said molecular constraints.

62. The method according to Claim 61 wherein steps (e) and (f) are repeated from 2-50 times.

